EXPEDITED PROCESSING REQUESTED: RESPONSE AFTER FINAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of)	Examiner: Shanon A. Foley
Dong Wang et al.)	Art Unit: 1648
Serial No.: 10/591,258)	Ref No.: 0685-P05150US01
Filed: November 28, 2006)	
For: "Macromolecular Delivery)	
Systems for Non-Invasive)	
Imaging, Evaluation and)	
Treatment of Arthritis and)	
Other Inflammatory Diseases")	

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.114

Introductory Comments

In response to the Official Action dated August 16, 2011, please amend the above-identified patent application as follows:

Amendments to the Claims:

Claim 1 (Original): A pharmaceutical composition for the treatment of an inflammatory disease comprising:

a water-soluble polymer and an effective amount of an anti-inflammatory therapeutic agent linked to said water-soluble polymer, wherein the water-soluble polymer specifically accumulates in sites of inflammation.

Claim 2 (Original): The pharmaceutical composition of claim 1, further comprising a targeting moiety linked to the water-soluble polymer.

Claim 3 (Cancelled)

Claim 4 (Previously Presented): The pharmaceutical composition of claim 1, wherein the water-soluble polymer is selected from the group consisting of a HPMA copolymer, polyethylene glycol, polyglutamic acid, polyaspartic acid, dextran, chitosan, cellulose, starch, gelatin, hyaluronic acid and derivatives thereof.

Claim 5 (Previously Presented): The pharmaceutical composition of claim 1, further comprising a bio-assay label linked to the water-soluble polymer.

Claim 6 (Previously Presented): The pharmaceutical composition of claim 1, further comprising a spacer between the therapeutic agent and the water-soluble polymer, wherein the spacer is cleavable.

Claim 7 (Previously Presented): The pharmaceutical composition of claim 1, further comprising a spacer between the therapeutic agent and the water-soluble polymer, wherein the spacer is uncleavable.

Claim 8 (Original): The pharmaceutical composition of claim 1, wherein the anti-inflammatory therapeutic agent is a glucocorticoid.

Claim 9 (Original): The pharmaceutical composition of claim 2, wherein the targeting moiety directs the composition to bone or cartilage.

Claim 10 (Previously Presented): The pharmaceutical composition of claim 2, wherein the targeting moiety is selected from the group consisting of bisphosphonates, quaternary ammonium groups, peptides, oligo-Asp, oligo-Glu, aminosalicylic acid, antibodies and fragments or derivatives thereof.

Claim 11 (Previously Presented): The pharmaceutical composition of claim 2, wherein the link between the targeting moiety and the water-soluble polymer is cleavable.

Claim 12 (Previously Presented): The pharmaceutical composition of claim 2, wherein the link between the targeting moiety and the water-soluble polymer is uncleavable.

Claim 13 (Previously Presented): The pharmaceutical composition of claim 1, wherein the water-soluble polymer comprises N-(2-hydroxypropyl)methacrylamide.

Claim 14 (Previously Presented): The pharmaceutical composition of claim 1, wherein the water-soluble polymer comprises one or more monomers selected from the group consisting of N-(2-hydroxypropyl)methacrylamide, N-isopropyl-acrylamide, acrylamide, N,N-dimethylacrylamide, N-vinylpyrrolidone, vinyl acetate, 2-methacryloxyethyl glucoside, acrylic acid, methacrylic, vinyl phosphonic acid, styrene sulfonic acid, maleic acid, 2-methacrylloxyethyltrimethylammonium chloride,

methacrylamidopropyltrimethylammonium chloride, methacryloylcholine methyl sulfate, N-methylolacrylamide, 2-hydroxy-3-methacryloxypropyltrimethyl ammonium chloride, 2-methacryloxyethyltrimethylammonium bromide, 2-vinyl-1-methyl-pyridinium bromide, 4-vinyl-1-methylpyridinium bromide, ethyleneimine, (N-acetyl) ethyleneimine, (N-hydroxyethyl) ethyleneimine, allylamine and combinations thereof.

Claim 15 (Previously Presented): The pharmaceutical composition of claim 1, wherein the therapeutic agent is selected from the group consisting of proteins, peptides, NSAIDs, DMARDs, glucocorticoids, methotrexate, sulfasalazine, chloriquine, gold, gold salt, copper, copper salt, penicillamine, D-penicillamine, cyclosporine, and mixtures thereof.

Claim 16 (Withdrawn): A method for the treatment of an inflammatory disease comprising:

administering the pharmaceutical composition of claim 1 to a subject thought to have an inflammatory disease; and

accumulating the pharmaceutical composition in inflamed tissue of the subject by the affinity of the water-soluble polymer for the inflamed tissue.

Claim 17 (Withdrawn): The method according to claim 16, further comprising targeting the water-soluble polymer to a specific tissue.

Claim 18 (Withdrawn): The method according to claim 16, wherein the inflammatory disease comprises rheumatoid arthritis.

Claim 19 (Cancelled)

Claim 20 (Withdrawn): The method according to claim 16, further comprising conducting a biodistribution assay wherein

the composition is labeled.

Claim 21 (Withdrawn): The method according to claim 16, further comprising cleaving the link between the therapeutic agent and the water-soluble polymer.

Claim 22 (Withdrawn): The method according to claim 17, wherein targeting the water-soluble polymer to a specific tissue comprises targeting bone or cartilage.

Claim 23 (Withdrawn): The method according to claim 17, wherein targeting the water-soluble polymer to a specific tissue comprises using a targeting moiety selected from the group consisting of bisphosphonates, quaternary ammonium groups, peptides, oligo-Asp, oligo-Glu, aminosalicylic acid, antibodies and fragments or derivatives thereof.

Claim 24 (Withdrawn): The method according to claim 17, further comprising cleaving a link between the targeting moiety and the water-soluble polymer.

Claim 25 (Withdrawn): A method of administering an aqueous composition to a subject, said method comprising:

administering the pharmaceutical composition of claim 1 in an aqueous solvent or diluent to a subject thought to have rheumatoid arthritis; and

allowing accumulation and targeting of the pharmaceutical composition in an arthrititic joint, thereby improving a treatment of arthritis.

Claim 26 (Withdrawn): The method according to claim 25, further comprising reducing a side effect of the therapeutic agent in tissues other than the arthritic joint.

Claim 27 (Withdrawn): The method according to claim 25, wherein the therapeutic agent is selected from the group

consisting of a NSAIDs, DMARDs, cycloxygenase-2 inhibitor, a glucocorticoid, a tumor necrosis factor blocker and an interleukin-1 receptor antagonist.

Claim 28 (Withdrawn): The method according to claim 25, wherein the water-soluble agent comprises a HPMA copolymer.

Claim 29 (Withdrawn): A composition for imaging and evaluating an inflammatory disease comprising:

a water-soluble polymer and an effective amount of a medical imaging agent linked to said water-soluble polymer, wherein the medical imaging agent is used in the imaging and evaluation of an inflammatory disease.

Claim 30 (Withdrawn): The composition of claim 29, further comprising a therapeutic agent linked to said water-soluble polymer.

Claim 31 (Withdrawn): The composition of claim 29, wherein the medical imaging agent is selected from the group consisting of at least one of a MRI, PET, CT and γ-scintigraphy agent.

Claim 32 (Withdrawn): The composition of claim 29, further comprising a targeting moiety linked to the water-soluble polymer.

Claim 33 (Cancelled)

Claim 34 (Withdrawn): The composition of claims 29, wherein the water-soluble polymer is selected from the group consisting of a HPMA copolymer, polyethylene glycol, polyglutamic acid, polyaspartic acid, dextran, chitosan, cellulose, starch, gelatin, hyaluronic acid and derivatives thereof.

Claim 35 (Withdrawn): The composition of claim 29, further

comprising a bio-assay label linked to the water-soluble polymer.

Claim 36 (Withdrawn): The composition of claim 29, further comprising a spacer between the imaging agent and the water-soluble polymer, wherein the spacer is cleavable.

Claim 37 (Withdrawn): The composition of claim 29, further comprising a spacer between the imaging agent and the water-soluble polymer, wherein the spacer is uncleavable.

Claim 38 (Withdrawn): The composition of claim 30, further comprising a spacer between the therapeutic agent and the water-soluble polymer, wherein the spacer is cleavable.

Claim 39 (Withdrawn): The composition of claim 30, further comprising a spacer between the therapeutic agent and the water-soluble polymer, wherein the spacer is uncleavable.

Claim 40 (Cancelled)

Claim 41 (Withdrawn): The composition of claim 32, wherein the targeting moiety directs the composition to bone or cartilage.

Claim 42 (Withdrawn): The composition of claim 40, wherein the targeting moiety is selected from the group consisting of bisphosphonates, quaternary ammonium groups, peptides, oligo-Asp, oligo-Glu, aminosalicylic acid, antibodies and fragments or derivatives thereof.

Claim 43 (Cancelled)

Claim 44 (Withdrawn): The composition of claim 29, wherein the water-soluble polymer comprises N-(2-hydroxypropyl) methacrylamide.

Claim 45 (Withdrawn): The composition of claim 29, wherein the water-soluble polymer comprises one or more monomers selected from the group consisting of N-(2-hydroxypropyl) methacrylamide, N-isopropylacrylamide, acrylamide, N,N-dimethylacrylamide, N-vinylpyrrolidone, vinyl acetate, 2-methacryloxyethyl glucoside, acrylic acid, methacrylic, vinyl phosphonic acid, styrene sulfonic acid, maleic acid, 2-methacrylloxyethyltrimethylammonium chloride, methacrylamido-propyltrimethylammonium chloride, methacryloylcholine methyl sulfate, N-methylolacrylamide, 2-hydroxy-3-methacryloxypropyltrimethyl ammonium chloride, 2-methacryloxyethyltrimethylammonium bromide, 2-vinyl-1-methylpyridinium bromide, 4-vinyl-1-methylpyridinium bromide, ethyleneimine, (N-acetyl)ethyl-eneimine, (N-hydroxyethyl)ethyleneimine, allylamine and combinations thereof.

Claim 46 (Withdrawn): The composition of claim 30, wherein the therapeutic agent is selected from the group consisting of proteins, peptides, NSAIDs, glucocorticoids, methotrexate, sulfasalazine, chloriquine, gold, gold salt, copper, copper salt, penicillamine, D-penicillamine, cyclosporine, and mixtures thereof.

Claim 47 (Withdrawn): A method for imaging and evaluation of an inflammatory disease, the method comprising:

administering the composition of claim 29 to the subject; and

imaging an inflammatory disease patient or animal model before and after the administration of the imaging agent with MRI, PET, CT or γ-scintigraphy equipment.

Claim 48 (Cancelled)

Claim 49 (Withdrawn): The method according to claim 47, further comprising conducting a biodistribution assay.

Claim 50 (Withdrawn): The method according to claim 47, further comprising targeting the water-soluble polymer to a specific tissue.

Claim 51 (Withdrawn): The method according to claim 50, wherein targeting of the compound is directed to bone or cartilage.

Claim 52 (Withdrawn): The method according to claim 50, wherein targeting the compound to a specific tissue comprises using a targeting moiety selected from the group consisting of bisphosphonates, quaternary ammonium groups, peptides, oligo-Asp, oligo-Glu, aminosalicylic acid, antibodies and fragments or derivatives thereof.

Claim 53 (Withdrawn): The method according to claim 50, further comprising cleaving a link between the targeting moiety and the water-soluble polymer.

Claim 54 (Withdrawn): The method according to claim 50, wherein imaging an inflammatory disease patient or animal model enhanced with the compound comprises imaging an arthritic joint.

Claim 55 (Cancelled)

Claim 56 (Cancelled)

Claim 57 (Original): The pharmaceutical composition of claim 1, wherein the therapeutic agent comprises a plurality of distinct therapeutic agents.

Claim 58 (Previously Presented): The pharmaceutical composition of claim 2, wherein the targeting moiety comprises a plurality of distinct targeting moieties.

Claim 59 (Original): The pharmaceutical composition of claim 58, wherein the plurality of distinct targeting moieties target a plurality of tissues.

Claim 60 (Original): The pharmaceutical composition of claim 5, wherein the bio-assay label comprises a plurality of distinct bio-assay labels.

Claim 61 (Previously Presented): The pharmaceutical composition of claim 6, wherein the spacer comprises a plurality of chemically distinct spacers.

Claim 62 (Withdrawn): The composition of claim 31, wherein the imaging agent comprises a plurality of distinct imaging agents.

Claim 63 (Withdrawn): The method according to claim 55, wherein the imaging agent comprises at least two imaging agents, wherein each of the two imaging agents is used in a different imaging technique.

Claim 64 (Withdrawn): A composition comprising a water-soluble N-(2-hydroxypropyl) methacrylamide copolymer linked to a targeting moiety and to a glucocorticoid via a pH sensitive hydrozone bond.

Claim 65 (Withdrawn): The composition of claim 64, wherein the glucocorticoid is dexamethasone.

Claim 66 (Withdrawn): The composition of claim 64, wherein the targeting moiety is hydrazine.

Claim 67 (Previously Presented): The pharmaceutical composition of claim 6, wherein the cleavable spacer comprises a hydrazone.

Claim 68 (New): A pharmaceutical composition for the treatment of an inflammatory disease consisting of:

1) a water-soluble polymer;

2) an effective amount of an anti-inflammatory therapeutic agent linked to said water-soluble polymer, optionally via a spacer;

3) optionally, a bio-assay label linked to said water-soluble polymer, optionally via a spacer; and

4) optionally, a targeting moiety label linked to said water-soluble polymer, optionally via a spacer;

wherein the water-soluble polymer specifically accumulates in sites of inflammation.

Remarks

The August 16, 2011 Official Action and the references cited therein have been carefully reviewed. In view of the following remarks and amendments, favorable reconsideration and allowance of this application are respectfully requested.

The present remarks and amendments are being filed as part of the submission required under 37 C.F.R. §1.114, in connection with the Request for Continued Examination, which is submitted concurrently herewith.

At the outset it is noted that a shortened statutory response period of three (3) months was set forth in the August 16, 2011 Official Action. Therefore, the initial due date for response is November 16, 2011.

The Examiner has rejected claims 1, 4, 5, 8, and 15 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent 5,356,633 (Woodle et al.) and Metselaar et al. (Arthritis and Rheumatism (2003) 48:2059-2066).

The Examiner has also rejected claims 2, 4, 6, 7, 9-14, 57-61, and 67 under 35 U.S.C. §103(a) as allegedly unpatentable over Woodle et al. and Metselaar et al. in view of Omelyanenko et al. (J. Controlled Rel. (1998) 53:25-37) and Smolen et al. (Nat. Rev. (2003) 2:473-488) and, optionally, in view of U.S. Patent Application Publication No. 2006/0127310 (Russell-Jones et al.).

Claims 1, 2, and 4-15 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. (Bioconjugate Chem. (2003) 14:853-859) and Metselaar et al.

Lastly, the Examiner has rejected claims 57-61 and 67 under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. and Metselaar et al. in view of Smolen et al. and Omelyanenko et al. and, optionally, further in view of Russell-Jones et al.

The foregoing rejections constitutes all of the grounds set forth in the August 16, 2011 Official Action for refusing the present application.

In accordance with the instant amendment, claim 68 has been added, which reads on the elected invention. Support for new claim 68 can be found throughout the application including, for example, in the original claims. No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §103(a) rejections of claims 1, 2, 4-15, 57-61, and 67, as set forth in the August 16, 2011 Official Action, cannot be maintained. These grounds of rejection are, therefore, respectfully traversed.

CLAIMS 1, 4, 5, 8, AND 15 ARE NOT RENDERED OBVIOUS BY WOODLE ET AL. AND METSELAAR ET AL.

The Examiner has rejected claims 1, 4, 5, 8, and 15 under 35 U.S.C. §103(a) as allegedly unpatentable over Woodle et al. and Metselaar et al. It is the Examiner's position that Woodle et al. "teach compositions comprising a hydrophilic biocompatible polymer, polyethylene glycol (PEG), in combination with anti-inflammatory agents, such as NSAIDs." The Examiner acknowledges that Woodle et al. do not disclose the anti-inflammatory glucocorticoids, but contends that it would have been obvious to a skilled artisan to replace the NSAIDs of Woodle et al. in view of the teachings of Metselaar et al.

Applicants continue to respectfully disagree with the Examiner's position for the reasons of record and those set forth below.

Claim 1 of the instant application, from which claims 4, 5, 8, and 15 depend, recites that the anti-inflammatory therapeutic agent is linked to a water-soluble polymer (hydrophilic polymer). In stark contrast, Woodle et al. describe using "vesicle-forming lipids" such as "amphipathic vesicle-forming lipids derivatized with a hydrophilic polymer" (see, e.g., column 3, lines 62-65).

Accordingly, the polymers of Woodle et al. are not water-soluble polymers as instantly claimed, but rather they comprise water-***in***soluble hydrophobic regions. Indeed, the polymer-derivatized lipids of Woodle et al. may be described as an amphiphilic polymer. By incorporating a hydrophobic lipid on the hydrophilic polymer, Woodle et al. have fundamentally changed the basic principles of the polymer, rendering it amphiphilic.

At page 3 of the instant Offcial Action, the Examiner states that "Woodle et al. clearly teach a hydrophilic biocompatible polymer, polyethylene glycol (PEG), in combination with anti-inflammatory therapeutic agents." Applicants respectfully submit that this is a clear mischaracterization of the whole teaching of Woodle et al. As explained above, Woodle et al. only disclose derivatized lipids that are amphiphilic. Woodle et al. do not teach or suggest the use of a water-soluble or hydrophilic polymer, as recited in the instant claims. Rather, Woodle et al. only disclose a derivatized amphiphilic entity.

Similarly, the "PEG liposomes" of Metselaar et al. are only PEG coated liposomes. Indeed, as explained at page 2060, the liposomes comprise a "PEG 2000-diasteroyl phosphatidyl ethanol amine (DSPE) conjugate", which is a PEG molecule conjugated to a lipid comprising a long hydrophobic chain. As such, the PEG-DSPE conjugate of Metselaar et al., like the derivatized lipids of Woodle et al., is not a water soluble polymer, as instantly claimed.

In view of the foregoing, it is evident that the references cited by the Examiner fail to teach or even suggest each and every element of the instantly claimed invention.

At page 4 of the instant Official Action, the Examiner states that "Applicant does not disagree with the assertion of obviousness to directly link an anti-inflammatory agent to a polymer." This is in correct. Indeed, Applicants argued that it was not obvious at pages 14 and 15 of the April 20, 2011 Official Action. Indeed, Applicants even stated at

page 14 that "Applicants respectfully disagree with the Examiner's position" with regard to the above point and provided reasoning over the next two pages.

As acknowledged by the Examiner, "neither Woodle et al. nor Metselaar et al. teach the PEG directly linked to the anti-inflammatory agent." Indeed, Woodle et al. and Metselaar et al. are clearly only describing formulations comprising a drug within a liposome. In stark contrast, the instant invention provides new "pro-drugs" wherein the drug is directly linked to the water-soluble polymer, thereby creating a new chemical entity. Moreover, the PEG molecules attached to the lipids of Woodle et al. and Metselaar et al. are not even proximal to the drug to be delivered. Indeed, the liposomes of Woodle et al. and Metselaar et al. would comprise a hydrophobic core with the drug surrounded by the derivatized lipids with the PEG molecules on the outside of the liposome. It would not be conceivable for a skilled artisan to link the therapeutic agent to the hydrophilic polymer, as recited in the instant claims.

Further, neither Woodle et al. nor Metselaar et al. provide the skilled artisan with any motivation to link the therapeutic agent with their derivatized lipids. Indeed, there is no teaching or suggestion in Woodle et al. and Metselaar et al. that a therapeutic agent linked to the derivatized lipid would be delivered to cells in the same fashion as the unlinked liposomes. Further, neither Woodle et al. nor Metselaar et al. teach or suggest that the therapeutic agent would retain activity upon linkage to the derivatized lipids. At page 4, the Examiner notes that Woodle et al. and Metselaar et al. teach the linkage of lipids to polymers. However, the linkage of the lipids to the polymer is merely for the generation of the carrier of the therapeutic agent. For the reasons stated hereinabove, Woodle et al. and Metselaar et al. fail to provide any motivation or expectation of success in linking the therapeutic agent to the derivatized lipids.

At page 5 of the Official Action, the Examiner states that "Woodle et al. clearly demonstrate sustained accumulation at target sites only when hydrophilic polymer-linked conjugates are used, see Figures 8B, 9, 10, and 11." Applicants respectfully disagree and submit that this is a mischaracterization of Woodle et al. As stated hereinabove, Woodle et al. only describe lipids derivatized with PEG. Moreover, Figures 8B, 9, 10, and 11 only demonstrate that the derivatized liposomes of Woodle et al. last longer in blood than non-derivatized lipids. The cited figures do not demonstrate sustained accumulation at a target site. Moreover, Woodle et al. fail to teach or suggest using anything other than liposomes for the delivery of a therapeutic agent (see, e.g., the Summary of the Invention). The Examiner has failed to provide any reason why the skilled artisan would forgo the basic tenant of liposomal delivery described by Woodle et al. (and Metselaar et al.) and only link the therapeutic agent to the hydrophilic polymer without the benefit of a liposome. Indeed, Woodle et al. teach the skilled artisan to use liposomes having "minimal leakage" (see, e.g., column 19). Moreover, Metselaar et al. teach the skilled artisan that therapeutic agents administered without liposomes are rapidly cleared and degraded. Metselaar et al. specifically state that the encapsulation of drug in liposomes "strongly influenced the pharmacokinetics of IV-injected glucocorticoiods" and that "liposomal encapsulation markedly enhanced the concentration of PLP in circulation" (page 2065). Metselaar et al. further state that "liposomal encapsulation protects PLP against conversion and degradation" and emphasize "the importance of a prolonged residence time in the circulation for the realization of sufficient joint localization" (page 2065). Since Metselaar et al. teach that liposome encapsulation is critical for prolonged residence time in circulation, it is self-evident that a skilled artisan would not look to eliminate the liposomes from the methods of Metselaar et al., as proposed by the Examiner.

Therefore, in view of the foregoing, it is without question that Woodle et al. and Metselaar et al. teach against using delivering an anti-inflammatory drug that is not entrapped or encapsulated within a liposome.

In addition to all of the above, the instant application demonstrates unexpectedly superior results in that the intravenous administration of the instantly claimed compositions targeted the site of inflammation in the host (e.g., in the rat ankle) and effectively delivered the anti-inflammatory drug to treat the inflammation. Indeed, at page 14 of the instant application, it is disclosed that 1 hour post-injection, HPMA conjugated to a contrast agent is already observed in sites of inflammation (see also Figure 3). In contrast, Metselaar et al. report that their derivatized liposomes were not present at sites of inflammation after 1 hour and appeared at inflammation sites only after 4 hours (see, e.g., Figure 2). Further, the instant application demonstrates that the administered HPMA conjugated to a contrast agent was "greatly reduced" in all vital organs and blood vessels after only 8 hours, while greatly increasing at points of inflammation (see page 15 and Figure 3). In stark contrast, Metselaar et al. show that the derivatized liposomes were highly retained in vital organs and sites without inflammation, particularly the spleen, even 48 hours after administration (Figure 2). Accordingly, the compositions of the instant invention clearly have unexpectedly superior properties over the prior art. Notably, a rejection under 35 U.S.C. §103 is proper only when the claimed inventions ***as a whole*** is shown to be obvious in view of the prior art. In that chemical compositions are inseparable from their properties, the properties of a claimed composition must also be considered as part of the "invention as a whole" when assessing the patentability under 35 U.S.C. §103. *In re Albrecht*, 185 USPQ 585 (CCPA 1975).

In view of all the foregoing, it is clear that Woodle et al. and Metselaar et al., considered alone or in

combination, fail to teach or suggest each and every element of the instantly claimed invention. Indeed, neither reference teaches a water-soluble polymer as instantly claimed nor the linking of a water-soluble polymer to an anti-inflammatory agent. Further, the instant application has demonstrated clear unexpectedly superior properties. In view of the foregoing, Applicants respectfully submit that the instant rejection is untenable. Withdrawal of the rejection is respectfully requested.

CLAIMS 2, 4, 6, 7, 9-14, 57-61, AND 67 ARE NOT RENDERED OBVIOUS BY WOODLE ET AL. AND METSELAAR ET AL. IN VIEW OF OMELYANENKO ET AL. AND SMOLEN ET AL. AND, OPTIONALLY, FURTHER IN VIEW OF RUSSELL-JONES ET AL.

The Examiner has also rejected claims 2, 4, 6, 7, 9-14, and 57-61 under 35 U.S.C. §103(a) as allegedly unpatentable over Woodle et al. and Metselaar et al. in view of Omelyanenko et al. and Smolen et al. The Examiner has also rejected claim 67 under 35 U.S.C. §103(a) as allegedly unpatentable over Woodle et al. and Metselaar et al. in view of Omelyanenko et al. and Smolen et al. and further in view of Russell-Jones et al. The Examiner acknowledges that Woodle et al. and Metselaar et al. fail to teach an HPMA copolymer-drug conjugate, using cleavable or uncleavable linkers, using specific targeting moieties, using a plurality of therapeutic agents, and using a plurality of distinct bio-assay labels. The Examiner contends that Omelyanenko et al. teach conjugates using targetable HPMA copolymer linked to an anti-cancer drug by cleavable and non-cleavable linkers. Smolen et al. allegedly teach that the efficacy of rheumatoid arthritis therapy is enhanced by using combination therapies. Russell-Jones et al. allegedly teach the use of a cleavable linker comprising hydrazone. It is the Examiner's position that it would have been obvious to a skilled artisan to combine these references to arrive at the instantly claimed invention.

Applicants respectfully disagree with the Examiner's

position for the reasons of record, those set forth above regarding Woodle et al. and Metselaar et al., and those set forth below.

As explained hereinabove, Woodle et al. and Metselaar et al. only disclose the use of encapsulated NSAIDs or glucocorticoids in liposomes formed by derivatized lipids. Further, Metselaar et al. stressed "the importance of a prolonged residence time in the circulation for the realization of sufficient joint localization" (page 2065). Omelyanenko et al. fail to teach or suggest that the HPMA-copolymer linked anti-cancer drugs have prolonged residence time in circulation. Rather, Omelyanenko et al. only perform *in vitro* experiments and are only concerned with the intracellular delivery of chemotherapeutic agents to cancer cells. The Examiner states at page 6 of the instant Official Action, that Omelyanenko et al. teach that "HPMA-bound-drugs increase drug concentrations inside cells." However, there is no teaching or suggestion that HPMA linked chemotherapeutic drugs would accumulate at sites of inflammation, as recited in the instant claims. Indeed, Metselaar et al. and Woodle et al. are concerned with the treatment of inflammation. As explained hereinabove, Metselaar et al. and Woodle et al. emphasize the importance of encapsulation of the drug in derivatized liposomes for increased retention in circulation for effective delivery to sites of inflammation. Significantly, Omelyanenko et al. do not teach or suggest that 1) HPMA linked drugs have prolonged residence time in the circulation; 2) HPMA linked drugs target sites of inflammation; or 3) that HPMA polymers are an equivalent substitute for PEG. In view of the foregoing, Omelyanenko et al. fail to provide the skilled artisan with the motivation or expectation of success in replacing the derivatized lipids of Metselaar et al. and Woodle et al. with an HPMA polymer and linking the therapeutic agent to the HPMA polymer. Indeed, it is noteworthy that the advantage provided by Omelyanenko et al. for using HPMA-copolymer conjugates is P-glycoprotein

efflux pump evasion, which is relevant to anti-cancer therapies and irrelevant to anti-inflammatory therapies.

Smolen et al. fail to supplement the deficiencies of the teachings of Metselaar et al., Woodle et al., and Omelyanenko et al. Indeed, Smolen et al. provide a review of therapeutic strategies for rheumatoid arthritis, but do not teach or suggest an anti-inflammatory therapeutic agent linked to a water-soluble polymer.

Lastly, the Examiner asserts that Russell-Jones et al. disclose a cleavable linker comprising hydrazone. However, Russell-Jones et al. clearly fail to supplement the deficiencies of the teachings of Metselaar et al., Woodle et al., and Omelyanenko et al., as set forth above.

In view of all the foregoing, Applicants respectfully submit that the instant rejection under 35 U.S.C. §103(a) is untenable. Withdrawal of the rejection is respectfully requested.

CLAIMS 1, 2, 4-15, 57-61, AND 67 ARE NOT RENDERED OBVIOUS BY WANG ET AL. AND METSELAAR ET AL., OPTIONALLY, IN VIEW OF SMOLEN ET AL. AND OMELYANENKO ET AL. AND, OPTIONALLY, IN FURTHER VIEW OF RUSSELL-JONES ET AL.

Claims 1, 2, and 4-15 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. and Metselaar et al. The Examiner has also rejected claims 57-61 under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. and Metselaar et al. in view of Smolen et al. and Omelyanenko et al. Claim 67 has also been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Wang et al. and Metselaar et al. in view of Smolen et al. and Omelyanenko et al. and further in view of Russell-Jones et al. It is the Examiner's position that it would have been obvious to a skilled artisan to combine the teachings of the cited references to arrive at the instantly claimed invention.

Applicants respectfully disagree with the Examiner's position for the reasons of record; those set forth above

regarding Metselaar et al., Smolen et al., Omelyanenko et al., and Russell-Jones et al.; and those set forth below.

At page 8 of the instant Official Action, the Examiner states that the "teachings of Metselaar et al. are required to teach motivation for combining glucocorticoids with a PEG carrier with a reasonable expectation of success." However, as explained hereinabove, Metselaar et al. do not suggest combining glucocorticoids with a PEG carrier and, in fact, teach away from such a combination. Indeed, Metselaar et al. only disclose the encapsulation of glucocorticoids in liposomes comprising derivatized lipids. Metselaar et al. teach that the encapsulation of the glucocorticoids in the liposomes is necessary for increased stability in blood which, in turn, is necessary for delivery to inflammation sites. Therefore, Metselaar et al. teach against using an anti-inflammatory drug in the absence of a liposome.

With regard to Wang et al., the reference is concerned with the delivery of bone therapeutic agents which promote the growth of bone. Wang et al. fail to teach or suggest that such linkages would be appropriate for the delivery of anti-inflammatory agents to inflammatory tissues. Notably, Wang et al. teach that with non-targeted HPMA and PEG polymers conjugated to FITC, no fluorescence labeling was observed near bone (page 857 and Figure 3). However, with the addition of a bone targeting moiety, the epiphysis (rounded ends of long bones) and diaphysis (main section or shaft of long bones) were labeled by the bone-targeting conjugates (page 857). Thus, Wang et al. teach that the bone-targeting conjugates bind bone outside of joints and that non-targeted conjugates are not present.

In stark contrast, the instant application demonstrates unexpectedly superior results in that the administration of the instantly claimed compositions targeted the site of inflammation in the host and effectively delivered the anti-inflammatory drug to treat the inflammation, as explained hereinabove.

In view of all of the foregoing, Applicants submit that the skilled artisan would have neither the motivation nor the expectation of success in combining the teachings of Metselaar et al. and Wang et al. to arrive at the instantly claimed invention.

For the reasons stated hereinabove, Smolen et al., Omelyanenko et al., and Russell-Jones et al. fail to supplement the deficiencies of Wang et al. and Metselaar et al.

In light of all the foregoing, Applicants respectfully submit that the instant rejections under 35 U.S.C. §103(a) cannot be reasonably maintained. Withdrawal of the rejections is respectfully requested.

CONCLUSION

In view of the foregoing remarks, it is respectfully urged that the rejections set forth in the August 16, 2011 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

If a fee is required or an overpayment is made, the Commissioner is authorized to charge or credit the deposit account of the undersigned, Account No. 04-1406.

Respectfully submitted,
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